REMARKS

The present amendments and remarks are submitted in conjunction with a Request for Continued Examination (RCE) and a Declaration under 37 CFR 1.132 by Dr. Jamila Louahed.

Reexamination and reconsideration of the above-identified application are requested in view of the following amendments and remarks.

1. Claims

Claims 113, 114, 116-125 and 145-156 are pending.

Support for the amendments to claim 113, 116, 117 and 146 is provided in the specification as filed, e.g. at paragraph 0045 which states that the term "protein" is used interchangeably with the term polypeptide and peptide; paragraphs 0060-0062 and 0071-0078, which discuss the immunogenicity of the ECD+PD (SEQ ID NO:6) or ECD+deltaPD (SEQ ID NO:7) polypeptides.

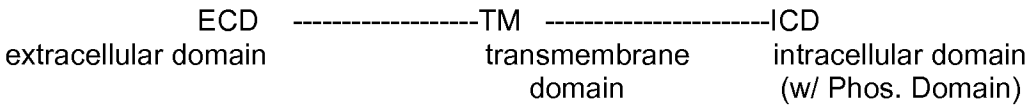
2. Rejection under 35 USC s. 112, second paragraph - Indefinite

Claims 113, 114, 116-125 and 145-156 stand rejected as indefinite. The Office Action states that it is unclear what is meant by the phrase "a protein comprising a contiguous amino acid sequence".

The Examiner cites the specification as defining "contiguous" as operably linked, for example "in the case of secretory leaders in reading frame" [0150]. The Examiner states that it is not clear whether and/or to what other protein the amino acid sequence of SEQ ID NO:6 or 7 should be contiguous, and that the phrase implies that the sequence of SEQ ID NO:6 or 7 should be fused with another protein.

Applicants did not intend the phrase 'contiguous' in the claims to imply that SEQ ID NO:6 or 7 must be fused to another amino acid sequence or protein. Rather, this phrase was used to establish that the amino acids of SEQ ID NO:6 or 7 were uninterrupted by any other sequence. Thus, for example, a full-length natural Her2/Neu protein does not contain the contiguous amino acids of SEQ ID NO:6 (or 7). As stated in the specification (at 008 and 009) and as represented below, human Her-2/neu is a transmembrane protein made of an

extracellular domain (ECD), a transmembrane domain, and a carboxy terminal intracellular domain (ICD). The ICD includes a phosphorylation domain (PD).



As described in the specification (e.g., at Figure 12) SEQ ID NO:6 consists of the human ECD sequence joined directly to the human PD sequence -- the Transmembrane Domain is omitted. Use of the phrase 'contiguous' was to establish that a full-length Her-2/neu protein (which contains the TM domain between the ECD and PD) is distinct from the amino acid sequence of SEQ ID NO:6 (ECD + PD).

This meaning of 'contiguous' is supported by dictionaries and issued patent claims (see e.g., US Patent Nos. 7,166,448 and 7,160,981). Stedman's Medical Dictionary (27th Edition) defines contiguous as "adjacent or in actual contact" (copy enclosed for Examiner's convenience).

To avoid confusion, the phrase 'contiguous' has been omitted from the claims as superfluous, as SEQ ID NO:6 is itself a contiguous amino acid sequence.

Applicants also respectfully disagree that the specification "defines the term 'contiguous' as 'operably linked'", as stated on page 6 of the Office Action. In paragraph 0150, the specification states:

> DNA regions are operably linked when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operably linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the polypeptide; a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation. Generally, "operably linked" means contiguous and, in the case of secretory leaders, in reading frame..

(underlining added)

Thus, while operably linked regions may be contiguous, Applicants submit that the specification does not define 'contiguous' as 'operably linked'.

Withdrawal of the present rejection is requested.

3. 35 USC 112, first paragraph: Written Description

Claims 113, 114, 116-125 and 145-156 stand rejected as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner concludes that "in the absence of structural characteristics that are shared by members of the genus of a 'protein' useful for eliciting or enhancing an immune response to Her-2/neu, one of skill in the art would reasonably conclude that the disclosure fails to provide a reasonable number of species to describe the genus." Applicants first respectfully submit that the standard is not whether one of ordinary skill in the art would conclude that *a sufficient number of species* had been presented, rather, the appropriate inquiry is whether the specification as of the filing date conveys with reasonable clarity to those skilled in the art that the applicant *was in possession of the claimed invention*. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. As further stated in MPEP 2163.04, if the examiner concludes that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of the filing of the application, "the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."

The Final Office Action states that the claims read on a genus of proteins which contain the contiguous amino acid sequence of SEQ ID NO:6 or 7, but that the specification does not disclose "any other proteins which contain a stretch of amino acid residues of SEQ ID NO:6 or 7." Therefore, the Examiner concludes, the claims encompass a genus of proteins "defined solely by a principal structural property, namely, that the protein contain a stretch of amino acids of SEQ ID NO:6 or 7, and which is simply a wish to know the identity of any material with that structural property."

Applicants respectfully dispute that the claims encompass a genus of polypeptides defined solely by structure. The claims are to a method of administering a polypeptide comprising SEQ ID NO:6 (or 7), where said sequence is provided *in an amount effective to elicit or enhance the immune response to HER-2/Neu*. Thus, there is a functional definition as well as a structural one; the structure of SEQ ID NO:6 (or 7) elicits or enhances the immune response to Her-2/Neu. As noted in MPEP 2163 (3(A)), an adequate written description of the invention may be shown by any description of sufficient, relevant,

identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (the written description "inquiry is a factual one and must be assessed on a case-by-case basis").

The Examiner further states that there is insufficient written description "because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a 'protein' are not set forth in the specification as filed, commensurate with the claimed invention." Applicants submit that sufficient relevant characteristics – both structure and function – are set forth in the specification. The exact sequence of both SEQ ID NO:6 and 7 is provided; the function of eliciting an immune response to Her2/Neu is also described and recited in the specification and claims. Applicants refer to paragraphs 0061-0062 and 0071-0078 of the specification.

As stated in paragraph 0061, in the present invention the ECD provides "structural conformation for inducing antibodies that react with HER-2/neu protein at the cell surface, while the ICD or PD increases the immunogenicity of the ECD". It is clearly stated that the ECD can be combined with the PD or the delta PD sequence (see e.g., paragraph 0062), and that the ECD and PDs are preferably human. Paragraph 0071 states:

> In a preferred embodiment, the present invention is directed to a fusion protein based on particular portions (e.g., HER-2/neu ECD-ICD fusion protein or HER-2/neu ECD-PD fusion protein) of the protein expression product of the HER-2/neu gene, which is capable of eliciting an antibody response and can be recognized by thymus-dependent lymphocytes ("T-cells").

Paragraph 0078 states:

> In a preferred embodiment, the ECD-PD fusion protein of the present invention comprises the HER-2/neu ECD fused directly to the HER-2/neu PD or to the HER-2/neu.DELTA.PD. Here and throughout the specification, a preferred embodiment of the fusion proteins of the invention is the HER-2/neu PD fusion protein.

Applicants submit that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicants were in possession of the invention that is now claimed. Possession of the claimed invention is established via words, structures, and figures in the specification that fully set forth the claimed invention.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by various means, including by disclosure of relevant, identifying characteristics, i.e., by functional characteristics coupled with a known or disclosed correlation between function and structure, sufficient to show the applicant was in possession of the claimed genus (see e.g., *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406). In the present claims, the functional characteristic (inducing an immune response) is directly related to the recited structure (SEQ ID NO:6 or 7).

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Applicants submit that one of ordinary skill in the art would recognize that applicants were in possession of the necessary common features of the members of the genus, in view of the disclosed species. Every member of the claimed genus must possess the disclosed structure, which is capable of eliciting an immune response (function). As further disclosed in the specification, the polypeptide may contain additional elements as are known in the art (see, e.g., paragraphs 0104-0105 regarding use of immunological enhancers as fusion partners).

Accordingly, the claims do not encompass widely variant species; all members of the genus share structure and function. Description of a representative number of species does not require a description that provides individual support for each species that the genus embraces.

Applicants submit that the present claims are supported by an adequate written description. The recitation of polypeptide structure and function in the present claims clearly conveys that the inventors were in possession of the claimed invention (polypeptide comprising the immunogenic SEQ ID NO:6 or 7) at the time the present application was filed. Withdrawal of the present rejection is requested.

4. Rejection under 35 USC 112, first paragraph: Enablement

Claims 114, 145, 155 and 156 stand rejected as non-enabled. Claims 114 and 145 have been canceled for purposes of advancing the prosecution of this application and should not be construed as acquiescence with regard to the Examiner's rejection; these amendments are made without prejudice to prosecution of such subject matter in a related divisional, continuation or continuation-in-part application.

The Office Action states that the specification is enabling for methods of eliciting an immune response using a Her-2/neu fusion protein comprising SEQ ID NO:6 or 7 to stimulate T-cell proliferation and cytotoxicity, and to induce B cells to produce an antibody, for use in treating malignancies such as breast, ovarian, colon, lung and prostate cancer. However, the Office Action states that the specification does not enable use of the method in humans, as recited in claims 155 and 156. Applicants traverse this rejection.

In support of the enablement rejection, the Office action states that "applicants have not demonstrated an immune response eliciting or enhancing effect of the fusion protein of SEQ ID NO:6 or SEQ ID NO:7 in a human, or with sufficient working examples of an animal model correlate" (page 10). The Office Action concludes:

> In view of the undue experimentation that would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for eliciting or enhancing a specific preventative or therapeutic immune response in subject much less that either protein of SEQ ID NO:6 or 7 could elicit or enhance an immune response in a human, the enablement provided by the specification is not commensurate in scope with the claimed invention. (page 10-11)

Applicants submit that the Examiner has not adequately established a *prima facie* case of non-enablement. As stated in MPEP 2164.04, the examiner has the initial burden to establish a reasonable basis to question enablement. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A specification which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to the claims must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained in the specification which are relied on for enabling support.

The Examiner states that no working examples are provided by the specification to show that SEQ ID NO:6 or 7 can elicit or enhance a human immune response to Her2Neu. The Examiner has not questioned whether one of skill in the art can make the compositions or polypeptides recited in the claims. The specification describes pharmaceutical compositions and routes of administration suitable for use in humans (see e.g., paragraphs

0011, 0206-0212). Various methods of detecting an immune response to Her2 are described, e.g. at paragraphs 0223 - 0236 of the specification.

As discussed in MPEP 2164, in an enablement rejection "it is incumbent upon the Patent Office … to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. As stated in MPEP 2164.04 (underlining added):

> This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. ….References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). <u>However, specific technical reasons are always required</u>.

The Examiner has not provided technical reasons or evidence in support of the non-enablement conclusion. Rather, the Examiner has merely cited a lack of working examples in the specification and concluded that undue experimentation would be required. The Office Action states "absent a specific and detailed description" in the specification of "how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for eliciting or enhancing a specific preventative or therapeutic immune response in a human", the claims are not enabled.

Applicants respectfully dispute that "a specific and detailed description" in the specification is required, as one skilled in the art would have a reasonable expectation of successfully practicing the claimed invention, based on the specification and the skill in the art at the time of filing. It is axiomatic that a patent need not teach, and preferably omits, what is well known in the art, and that some experimentation is acceptable as long as it is not undue.

Applicants refer to the review article by Kurebayashi submitted herewith (published Jan. 01, but accepted July 2000) as evidence of the state of the art at the time the

specification was filed. This article describes the Her2 signaling pathway, the oncogenic potential of Her2 overexpression, and Her2 overexpression as a therapeutic target (see e.g., page 49, end of first column continuing to second column).

Applicants refer to the Abstract by Limentani et al., published in the Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings, Vol. 24, No. 18S (June 20 Supplement), 2006:631, and the Poster by Limentani et al., presented at the 18th EORTC-NCI-AACR Symposium, Nov. 7-11 2006 , Prague, CZ (conference organized by the European Organization for Research and Treatment of Cancer (EORTC) in conjunction with the National Cancer Institute (NCI) and the American Association for Cancer Research (AACR)).

The ASCO Abstract reports on a dose escalation study (GSK Study ID 719125/002 (National Clinical Trials identifier NCT00058526)) of a recombinant Her2 protein, used as an adjuvant treatment for Stage II or Stage III Her2 positive breast cancer in human patients. The EORTC-NCI-AACR Poster reports on the same study as the Abstract, as well as a Phase II study of metastatic Her2 positive breast cancer in human patients (GSK Study ID 100633 (National Clinical Trials Identifier NCT00140738)).

A Declaration is submitted herewith by Jamila Louahed, an author on both the Abstract and the Poster, stating that the recombinant Her2 protein described in the Abstract and the Poster was the 919 amino acid sequence disclosed in the specification as SEQ ID NO:6. The Declaration further notes that the recombinant protein was administered with adjuvant AS15, which is a combination of a CpG-containing oligonucleotide (CpG7909), monophosphoryl lipid A, and a saponin derivative (QS-21. The specification at paragraph 0210 discusses these adjuvant components, and states that an enhanced system involves the combination of monophosphoryl A and a saponin derivative. (AS15 is also referred to by some sources as SB-AS15).

These post-filing publications are cited as evidence of the level of skill in the art as of the application filing date, and as evidence that the method disclosed in the application is enabled by the specification. The Declaration is submitted to establish that the materials used in the reported clinical studies are commensurate in scope to what was disclosed in the specification. Applicants submit that one of skill in the art, using the teachings of the specification combined with contemporary immunotherapy and clinical trials practices,

would have been able to successfully make and use the claimed invention without undue experimentation, as evidenced by the Abstract and Poster discussed above.

Withdrawal of the present rejection is requested.

Conclusion

Applicants respectfully submit that the present application is in condition for allowance. If the Examiner believes a telephone conference would expedite prosecution of the application, please do not hesitate to call the undersigned at 919-483-1012.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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Enc: Stedman's Medical Dictionary (27th Edition): contiguous
Declaration of Dr. Jamila Louahed under 37 CFR 1.132